

U.S. Patent Application No. 09/756,978  
Response to Office Action Dated 25 November 2003

Remarks

Claims 1-66, 81, and 83 are pending in the application. Claim 82 has been canceled. Claims 1, 66, 81, and 83 are the only independent claims pending after entry of this Amendment. This Amendment contains no new matter.

The Applicant is frustrated that two consecutive Examiners of this application have evidently failed to understand the methods that are disclosed and claimed. Careful consideration of THE SUBJECT MATTER THAT IS CLAIMED is requested.

The Applicant appreciates the courtesies extended by Examiners Yu and Chen during the personal interview conducted at the USPTO's Carlyle campus on 18 May 2004, by Examiner Caputa during the 20 May 2004 telephone interview, and by all three examiners during the 3 June 2004 personal interview conducted at the USPTO's Carlyle campus. The Applicant's summaries of the 18 and 20 May interviews have already been submitted, and the Applicant's summary of the 3 June 2004 interview will be submitted in the near future.

Each of the Examiner's objections or rejections is addressed below in the order they were presented in Paper No. 27.

**Rejection Pursuant to 35 U.S.C. § 112, First Paragraph**

Claims 2 and 4-6 stand rejected pursuant to 35 U.S.C. § 112, first paragraph. In the Examiner's view, the claimed methods involve use of proteases to induce death of tumor cells. The Examiner asserts that proteases would not be expected to kill tumor cells.

The Applicant respectfully urges the Examiner to overcome her fixation with regard to whether a protease can or will kill a tumor cell. It is absolutely immaterial TO THE CLAIMED INVENTION whether a protease will kill a tumor cell.

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As recited in the rejected claims, proteases are but one example of "antigen-releasing agents" disclosed in the specification (see page 13, line 25, through page 14, line 7). The role of an antigen-releasing agent in the claimed methods is simply to induce release of antigens from the surface of tumor cells. The claims do not require that a protease on its own be able to kill a tumor cell. The ONLY role that a protease need fulfill in claims 2 and 4-6 is to release one or more antigens from cells of a tumor when locally administered thereto.

The Applicant **INSISTS** that the Examiner cease reading into these claims a limitation that is not recited therein.

During the 18 May 2004 interview, the Examiners suggested that local administration of a protease to a tumor could lead to growth, spread, or metastasis of the tumor. The Applicant respectfully contends that it is irrelevant to enablement whether local administration of a protease to a tumor will have the side effects suggested by the Examiner. The Examiner appears to be confusing the requirements for obtaining a patent with the requirements for obtaining government approval for marketing drugs. The **INVENTION THAT IS CLAIMED** does not recite an absence of tumor growth, spread, or metastasis. Instead, claims 2 and 4-6 recite a method of inducing tumor cell death (i.e., regardless of whether some tumor cells may grow, spread, or metastasize).

The Examiner's contention that administration of a protease to a tumor could lead to growth, spread, or metastasis of the tumor is completely unsupported, and is contradicted by two references submitted with this Amendment – Wald et al., 1998, Life Sciences 62(3):PL43-PL48 and Kuriyama et al., 2001, Cancer Res. 61:1805-1809. The Wald reference discloses that a rectally-administered combination of proteases decreased metastasis of an implanted melanoma xenograft in mice. Similarly, the Kuriyama reference discloses that no increase in tumor metastasis could be detected when trypsin (a protease) locally injected into glioblastoma xenografts. The Applicants respectfully contend that there is no reason to believe that a protease locally administered to a tumor will lead to growth, spread, or metastasis of the tumor, as asserted by the Examiner. This contention is in addition to the Applicant's contention that it is immaterial (as regards

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enablement of the claimed invention) whether such growth, spread, or metastasis would occur following local administration of a protease.

The Examiner must withdraw the rejection of claims 2 and 4-6 pursuant to 35 U.S.C. § 112, first paragraph.

**Rejection Pursuant to 35 U.S.C. § 103(a) Over Lee in View of Tannenbaum or Lanni**

The Examiner rejects claims 1, 3, 13-17, 19, 20, 25-29, 31-39, and 81-83 pursuant to 35 USC 103(a) over Lee in view of either Lanni or Tannenbaum.

In the Amendment and Request for Reconsideration filed by the Applicant on 11 August 2003, the contents of the Lee, Tannenbaum, and Lanni references were discussed in detail. Those discussions are incorporated into this response by reference.

The Applicant respectfully contends that the Examiner severely mischaracterizes or misunderstands the teachings of these three references, as they are applicable to the pending claims. For reasons discussed below, there is no motivation to combine the cited references and, even if they are combined, the cited references fail to teach every recitation of the claimed invention.

Lee

The Applicant respectfully contends that the Examiner mischaracterizes or misunderstands the Lee reference in at least several ways.

First, the Examiner asserts that Lee's use of IFN-g, TNF, and anti-Fas antibody is relevant to the claimed methods, which are directed to inducing tumor cell death IN A HUMAN PATIENT. The Examiner refers to Figure 1C in Lee, relating to administration of these three agents to cultured RENCA tumor cells. The Examiner also refers to page 232, right column, line 5, relating to peritumoral administration of anti-Fas antibody (ONLY!) to RENCA tumors implanted into mice. The Examiner asserts that these combined teachings of Lee are relevant to locally administering IFN-g, TNF, and anti-Fas antibody to a tumor in a patient. However, this is a mischaracterization of Lee.

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Lee uses IFN-g and TNF only in in vitro experiments in which tumor cells are cultured outside of an animal (i.e., outside of a system in which there is normally a basal level of IFN-g and TNF expression). As disclosed in Lee (see first paragraph, page 238, endogenous IFN-g production was known to be necessary to facilitate Fas-mediated tumor cell apoptosis. Lee added IFN-g and/or TNF only to tumor cells grown *in vitro* - LEE DID NOT ADMINISTER (LOCALLY OR OTHERWISE) IFN-g OR TNF TO ANY ANIMAL IN WHICH TUMOR CELLS HAD BEEN IMPLANTED. Indeed, Lee showed that IFN-g knockout mice exhibit significantly less (see Figure 7A) Fas-mediated tumor cell apoptosis. The clear implication to any skilled artisan is that normal, endogenous levels of IFN-g and TNF were considered by Lee to be sufficient to facilitate whatever Fas-mediated apoptosis-inducing effects might be attributable to anti-Fas antibodies. Lee does not teach or suggest co-administering (locally or otherwise) all three of IFN-g, TNF, and anti-Fas antibodies to animals.

Thus, even if anti-Fas antibody were considered to be an "antigen-releasing agent" as recited in the claims, Lee does not teach co-administering anti-Fas antibody and any other compound TO AN ANIMAL. The Examiner's rejection is improper for this reason alone.

Second, the Examiner asserts that anti-Fas antibody is an "antigen-releasing agent" in the sense of the claimed invention. Evidently, the Examiner believes that administering anti-Fas antibody to an animal will result in death of at least some tumor cells and release of antigens therefrom<sup>1</sup>. Even if these assertions are correct, ANTI-FAS ANTIBODY IS INOPERATIVE AS AN EMBODIMENT OF AN ANTIGEN-RELEASING AGENT IN THE CLAIMED INVENTION.

Fas is a transmembrane protein which induces a chain of events resulting in apoptosis when Fas binds with either FasL (another cell-surface protein) or with certain anti-Fas antibodies. FAS IS EXPRESSED BY LEUKOCYTES<sup>2</sup>, including by

<sup>1</sup> As indicated in the enclosed reference by Kim et al. (1999, Arch. Pathol. Lab. Med. 124(5):687-693), Fas is expressed on a wide variety of cell types, including at least some tumor cells.

<sup>2</sup> See page 72, right column, first full paragraph of Parslow, 1997, "The Immune Response," In: Medical Immunology, Stites, et al., Eds., Appleton & Lange, Stamford, CT; copy enclosed.

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activated T cells (i.e., which are known to be involved in type 1 inflammatory responses). If an anti-Fas antibody were administered locally to a tumor, leukocytes at the tumor site would be induced to apoptose. As explained throughout the specification, the claimed invention relates to inducing the immune system to mount a (leukocyte-mediated) anti-tumor inflammatory response. If anti-Fas antibody were used as the "antigen-releasing agent" in the claimed invention, the invention would be inoperative. The skilled artisan would understand that anti-Fas antibody cannot be used in a method in which the activity of leukocytes are required.

Third, Lee does not even teach that anti-Fas antibodies can be used to kill tumor cells. Figure 11 of Lee discloses an experiment in which (Fas-bearing) RENCA tumor cells were implanted into mice. Open circles represent RENCA-implanted mice to which a control (i.e., non-Fas-binding) antibody was administered, and filled circles represent RENCA-implanted mice to which a Fas-binding antibody was administered. If anti-Fas antibodies exhibited tumor-killing efficacy, then a skilled artisan would expect that the RENCA-implanted mice to which the Fas-binding antibody was administered would live longer (i.e., that the tumor would be slowed). In fact, the opposite effect was achieved - mice receiving anti-Fas antibodies died SOONER than did mice that received control antibody. The only mice which appeared to benefit from anti-Fas antibody administration were mice into which had been implanted RENCA tumors that had been engineered to overexpress Fas. The Examiner's assumption that anti-Fas antibodies will exhibit antigen-releasing activity from non-engineered tumors is not supported by the Lee reference.

In summary, Lee does not teach administering IFN-g, a second IR1-promoting agent, or a leukocyte attractant to any animal. Lee also fails to teach administering any antigen-releasing agent that would be operative in the claimed invention.

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Tannenbaum

Tannenbaum recognized that systemic administration of IL-12 induced an anti-tumor response that required endogenous levels of IFN-g, IP-10, and Mig.

Tannenbaum discloses systemic administration of IL-12 (a "second IRI-promoting agent" in the claimed invention) to RENCA tumor-implanted mice, but does not disclose administration of any of IFN-g, IP-10, and Mig. Tannenbaum does not disclose any of:

- administering an antigen-releasing agent to any animal;
- administering IFN-g to any animal;
- administering a leukocyte attractant to any animal; and
- locally administering any compound to a tumor in an animal.

The Examiner has provided no motivation for combining Tannenbaum with any other reference beyond a vague assertion that "*all of the products in the instant claim have been shown to have good effects [sic] in cancer treatment and/or for cancer patients*" (Paper No. 27, page 5, second full sentence). Regardless of which "good effects" the Examiner is referring to, the Examiner has not provided any reason why a skilled artisan would select the particular interactive combination of agents recited in the claims and administer them locally to a tumor in a human patient. Absent such motivation, the Examiner's combination of Tannenbaum with Lee (and Lanni, discussed below) is merely a hindsight reconstruction of the claimed invention. The Examiner has provided no reason why a skilled artisan would consider Lee and Tannenbaum to have any relation to one another.

Lanni

The Examiner asserts that Lanni teaches "*that it is well known in the art that combination therapy have been [sic] used to minimize and/or avoid chemotherapeutic resistance by tumor cells*" (Paper No. 22, page 4, fifth full sentence - there is no explanation of Lanni in Paper No. 27). However, this is not accurate. LANNI DOES NOT DISCLOSE ANY COMBINATION of active agents. The Examiner refers to the abstract and Figure 3 of Lanni, but neither describes administration of more than one anti-tumor agent. Lanni describes use of conditioned medium obtained from cultured

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macrophages treated with either paclitaxel or cephalomannine to induce apoptosis in Ras-transformed fibroblast cells *in vitro*, and also describes the ability of several antibodies to neutralize the activity in such conditioned media.

Lanni does not disclose any of:

- administering an antigen-releasing agent to any animal;
- administering IFN-g to any animal;
- administering a second IR1-promoting agent to any animal;
- administering a leukocyte attractant to any animal; and
- locally administering any compound to a tumor in an animal.

The Examiner has provided no motivation for combining Lanni with any other reference beyond the vague assertion mentioned above. The Examiner has not provided any reason why a skilled artisan would select the particular interactive combination of agents recited in the claims and administer them locally to a tumor in a human patient. Absent such motivation, the Examiner's combination of Lee and Tannenbaum with (or in view of) Lanni is not permitted. The Examiner has provided no reason why a skilled artisan would consider Lee and Tannenbaum to have any relation to one another or to Lanni.

Thus, even in combination, Lee, Tannenbaum, and Lanni fail to teach any of:

- administering to any animal an antigen-releasing agent that is operative in the claimed invention;
- administering IFN-g to any animal;
- locally administering a second IR1-promoting agent to any animal;
- administering a leukocyte attractant to any animal; and
- locally administering to a tumor in an animal any compound that is operative in the claimed invention.

For this reason, combining Lee with either or both of Tannenbaum and Lanni fails to teach every element of the invention that is claimed, and the Examiner's obviousness rejection is in error.

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The Examiner's purported motivation for combining the Lee, Tannenbaum, and/or Lanni references is, essentially, that it is known that anti-tumor treatments can be combined. However, this reasoning fails in at least two regards. First, Lee does not teach any therapeutic effect. Lee simply teaches that anti-Fas antibodies can kill tumor cells that are induced to overexpress Fas. Second, none of the references cited by the Examiner discloses or suggests combining the teachings of the particular references cited by the Examiner. Instead, the Examiner appears to be simply picking elements from the prior art on the basis of the 'recipe' supplied in the Applicant's specification, which is improper.

For the foregoing reasons, the Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 1, 3, 13-17, 19, 20, 25-29, 31-39, and 81-83 pursuant to 35 USC 103(a) over Lee in view of either Lanni or Tannenbaum.

**Rejection Pursuant to 35 U.S.C. § 103(a) Over Lee in View of Tannenbaum or Lanni and Further in View of Other References**

The remainder of the Examiner's 35 U.S.C. § 103(a) rejections (relating to claims 7-12, 17, 18, 30, 40-66, and 81-83) rely on Lee + (Tannenbaum or Lanni) + (another reference). None of the other references correct the deficiencies of the Lee, Tannenbaum, and Lanni references, and the Examiner's rejection of these claims is improper for the same reasons referenced above. Reconsideration and withdrawal of the Examiner's rejection of claims 7-12, 17, 18, 30, 40-66, and 81-83 pursuant to 35 U.S.C. § 103(a) are requested for that reason.

**Double Patenting**

The Examiner rejects claim 82 as being a substantial duplicate of claim 1. Claim 82 has been canceled, and the Examiner's rejection is believed to be moot.

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**Summary**

For the reasons set forth above, the Applicant respectfully contends that each of claims 1-66, 81, and 83 are in condition for allowance. Prompt issuance of a Notice of Allowance is respectfully requested

Respectfully submitted,

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